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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/177,814	10/23/1998	TERRY L. GILTON	353OUS(97-12	3621

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/177,814	GILTON, TERRY L.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13-44,46,48-64,66-74 and 105-107* is/are pending in the application.

4a) Of the above claim(s) *30-44,46,48-64,66-74 and 105-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 13-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-11,13-44,46,48-64,66-74 and 105-107* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group 1, claims 1, 3-11, and 13-29, without traverse, filed 5/10/04 is acknowledged and has been entered. Claims 30-44, 46, 48-64, 66-74 and 105-107 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Accordingly, claims 1, 3-11, 13-44, 46, 48-64, 66-74 and 105-107 are pending. Claims 1, 3-11, and 13-29 are under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1, 3-5, 7, 9-11, 13, 16, 18-20, 22-25, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Northrup et al. (US 5,882,496) for reasons of record.

Isaka et al. disclose a chromatograph apparatus comprising a microchannel element formed on a semiconductor substrate. Specifically, the apparatus includes a semiconductor substrate and a matrix (microchannel) which extends across the substrate. The semiconductor substrate comprises of silicon (see column 6, lines 5-7). The matrix is formed with a desired pattern, i.e. linear, circular, on the semiconductor substrate by incorporating a porosity thereon in order to create a porous portion with increased pore size and extended branching of the pores on the semiconductor surface (see Abstract and column 1, lines 35-46). The length of the matrix channel is not limited although its length is preferably larger than its diameter (see column 2, lines 18-25). The porosity is preferably 10-90% (see column 2, lines 60-63). Optimal pore size and pore shape can be achieved in accordance with the substance to be separated and measured, i.e. selecting the type and concentration of a dopant (see column 3, lines 35-42). A thin semiconductor substrate layer may be formed by ion injection after formation of a silicon dioxide layer by thermal oxidation (see column 4, lines 53-55). The apparatus is applicable for use in solid-gas separation, solid-liquid separation, liquid-liquid separation, and gaseous separation. The separation makes use of the difference in flow rate between gases and liquids or in reactions (enzyme reaction)

involving capture substrate (absorptivity involving immobilized enzyme) (see column 3, lines 1-14 and 50-54). In liquid chromatographs, an inlet port of the apparatus is coupled to a pump (migration facilitator) into the porous channel to identify difference in elution time between two liquids using differential refractometer (see column 5, lines 17-29). Isaka et al. also disclose ion column detection performed on a capillary, i.e. absorption detector (see column 3, lines 16-24). Finally, Isaka et al. teach incorporation of a sealing element (cover) consisting of a single-crystal silicon film on the silicon substrate on which the matrix is formed (see column 5, lines 38-49).

Isaka et al. differ from the instant invention in failing to teach forming at least two porous microchannels in the silicon substrate. Isaka et al. further differs from the instant invention in failing to teach the migration facilitator as comprising electrodes disposed into the porous region of the chromatograph.

Northrup et al. disclose porous silicon electrophoresis and control flow devices. Porous silicon increases surface area and also increases gas or fluid flow in flow channel structures designed to capture (adsorb, separate or filter) biological particles from a sample (see Abstract and column 7, lines 38-50). Northrup et al. specifically disclose that porous silicon which is fabricated from crystalline silicon have very small pore diameters so that they can be produced with relatively high degree of uniformity and control (see column 1, lines 27-55). Porosity is formed by electrochemical etching to form small pores in the bulk silicon (see column 3, lines 54-60). Figure 8 illustrates an electrophoresis device having formed thereon, multiple, distinct, unconnected porous silicon columns or spaced members. A negative electrode is formed at one end (inlet)

of the porous silicon columns and a positive electrode is formed at an opposite end (outlet) of the porous silicon columns, thereby forming microelectrophoresis channels (see column 7, lines 38-50). These electrodes or migration facilitators within or adjacent the porous membrane are used to control flow of specific electrically charged biochemical species (see column 5, lines 21-67). Because of its high surface area and specific pore size, porous silicon is utilized for a variety of applications on a miniature scale for significantly augmenting adsorption, vaporization, desorption, condensation, and flow of liquids and gasses while maintaining the capability of modification such as being doped or coated using conventional integrated circuit and micromachining (see Summary).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate multiple porous silicon columns as taught by Northrup into the miniaturized chromatograph apparatus of Isaka because Northrup specifically taught multiple columns because duplication of parts such as in this case, columns in separation flow devices, is conventional and well within ordinary skill. Additionally, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate electrodes such as taught by Northrup into the miniaturized silicon device taught by Isaka because Northrup specifically taught application of electrodes into miniaturized porous silicon structures in electrophoresis devices such as in the miniaturized separation device taught by Isaka.

3. Claims 8 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Northrup et al. (US 5,882,496) as applied to claims 1, 3-5, 7, 9-11, 13, 16, 18-20, 22-25, and 29 above, in further view of Swedberg et al. (US 5,571,410) for reasons of record.

Isaka et al. and Northrup et al. have been discussed supra. Isaka et al. and Northrup et al. differ in failing to teach antibody or antigen as the capture substrate for the miniaturized chromatograph.

Swedberg et al. teach a miniaturized planar column device for integrated sample analysis of analytes (see column 8, lines 5-38). Swedberg et al. specifically teach a stationary phase (sample treatment component) which performs a filtration function filled with a biocompatible porous medium of particles into which a capture function has been incorporated therein (see column 27, lines 33-61 and Example 1). Specifically, Swedberg teaches a stationary phase incorporated into a miniaturized affinity chromatography column onto which separation and capture functions are combined; the capture species (biological affiants) include antibodies, antigens, lectin, enzyme etc. (see column 27, lines 43-61 and Example 1). Swedberg et al. also disclose a "LIGA" process which is used to refer to a process of fabricating microstructures having high aspect ratios and increased structural precision in order to create desired uniformity in microstructures such as channel ports, apertures, and microalignment means (see column 13, lines 9-33).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the stationary phase in the porous matrix taught by Isaka, having

multiple columns as modified by Northrup, to include antigens and antibodies as taught by Swedberg in order to achieve performance of both filtration and capture function because Swedberg specifically suggested potential application of his teachings in monitoring biological analyses as applied to liquid phase separation devices in the miniature scales such as the device taught by Isaka. One of ordinary skill in the art would have been motivated to incorporate the teachings of Isaka as modified by Northrup, with biocompatible modification as taught by Swedberg because both of Isaka and Northrup specifically taught that porous silicon has established porosity with enhanced capacity for separation, augmented adsorption, differentiation of flow rate in liquid or gaseous samples, thereby producing a highly versatile miniaturized chromatographic device capable of both enhanced partitioning and complexation reactions.

4. Claims 14-15, 17, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Northrup et al. (US 5,882,496) as applied to claims 1, 3-5, 7, 9-11, 13, 16, 18-20, 22-25, and 29 above, and further in view of Miura et al. (US 5,132,012) for reasons of record.

Isaka et al. and Northrup et al. have been discussed supra. Isaka et al. and Northrup et al. differ from the instant invention in failing to teach incorporating a field effect transistor detector, memory device, and controls into the apparatus.

Miura et al. disclose a miniaturized sample separator in the form of a liquid chromatograph comprising an analyzing chip in which the capillary flowpath is formed in

a substrate and a field effect transistor detector disposed downstream of the capillary (see Abstract). The substrate is made of silicon and further has an insulative membrane formed of silicon dioxide (see column 3, line 51 to column 4, line 7). Both the column for separation and the field effect transistor detector are formed integrally with the substrate. After the silicon oxide layer has been formed on the capillary groove, a stationary phase is formed. A valve is connected to a first end of the flow path in the sample application area (sample introduction pipe) where a sample is selectively introduced into the flowpath. A separation carrier solution (carrier gas/ vacuum source) is fed under pressure by a feed pump and then discharged from a drain after having passed through the flowpath. Miura et al. further teach a sealing element (seal plate) such as borosilicate glass for sealing the opening portion of the groove portion to define the flow passage for a liquid sample. The liquid chromatograph also comprise a memory (control) device and an output device such as a data processor which is connected to the detector for detecting separated constituents (see column 5, line 63 to column 6, line 22). Figures 4A and 4B illustrate an electrical conductivity detector which comprise voltage application and current detection components, i.e. electrodes. Figure 9 shows a schematic view of the overall flow passage of the liquid chromatograph.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate field effect transistor detector, memory device, and controls as taught by Miura into the miniaturized chromatograph apparatus with porous silicon channels such as taught by Isaka as modified by Northrup, because Miura

specifically taught application of such elements into miniaturized chromatographic devices such as taught by Isaka and Northrup. One of ordinary skill in the art at the time of the invention would have been motivated to combine the teaching of Miura into the chromatograph device of Isaka as modified by Northrup, because Miura recognized and solved technical difficulties in miniaturizing analyzers by incorporating these necessary elements into his device (rather than providing them independently of each other).

5. Claims 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Northrup et al. (US 5,882,496) as applied to claims 1, 3-5, 7, 9-11, 13, 16, 18-20, 22-25, and 29 above, and in further view of Sunzeri (US 5,536,382) for reasons of record.

Isaka et al. and Northrup et al. have been discussed supra. Isaka et al. and Northrup et al. differ from the instant invention in failing from the instant invention in failing to incorporate a control column into the separation devices comprising porous silicon.

Sunzeri discloses analysis of constituents of human biological fluids using capillary electrophoresis. Sunzeri specifically teaches the use of standard control to provide a standard for quantitation (see column 9, lines 28-67). Sunzeri further teaches that quantitation using internal and external standards is beneficial in assays where the sample matrix affects fluorescence sample quenching (see column 10, lines 1-34).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate internal standards or controls as taught by Sunzeri, into the miniaturized chromatographic device taught by Isaka as modified by Northrup, because internal controls or standards in column chromatographic devices are conventional and are standard laboratory practice to those well within ordinary skill.

Response to Arguments

6. Applicant's arguments filed 1/26/04 on claims 1, 3-11, and 13-29 have been fully considered but they are not persuasive.

A) Applicant argues that the combination of Isaka et al. with Northrup et al. does not suggest or render obvious the claimed invention. Applicant contends that both Isaka and Northrup do not teach or suggest "a detector fabricated on said substrate" as recited in claim 1 and the absorption detector as taught by Isaka is located downstream of another separate conventional capillary column.

Contrary to Applicant's argument, absorption detector or fluorescence detector is taught by Isaka in column 3, lines 15-24 as cited, and its fabrication on the substrate for detection "inside the microchannel element" so as to be in communication with the porous capillary regions, is suggested in column 2, lines 63-67 of Isaka.

B) Applicant argues that Northrup et al. does not teach or suggest a "detector fabricated on said substrate" and Isaka et al. does not teach or suggest more than a

single column; therefore, the combination of Isaka et al. with Northrup et al. does not suggest or render obvious the claimed invention.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the rejection is based on the combination of Isaka with Northrup as discussed supra. Isaka discloses an absorption detector which is suggested to be fabricated on the claimed substrate and Northrup discloses and illustrates an electrophoresis device having formed thereon, multiple, distinct, unconnected porous silicon columns or spaced members. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate multiple porous silicon columns as taught by Northrup into the miniaturized chromatograph apparatus of Isaka having a detector formed on a substrate because Northrup specifically taught multiple columns and because duplication of parts such as in this case, is conventional and well within ordinary skill.

C) Applicant argues that the combination of Isaka et al. and Northrup et al. with Swedberg et al. does not suggest or render obvious claims 8, 26 and 28. Applicant specifically contends that Swedberg teaches away from the use of silicon or silicon dioxide, and does not teach or suggest a "detector fabricated on said substrate" or

"porous matrices formed in the substrate ... comprising at least two distinct, unconnected capillary columns."

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Swedberg et al. is incorporated with the teaching of Isaka and Northrup only for the teaching of a reaction region or capture component comprising an antigen or an antibody. In as far as the use of silicon as substrate for immobilization of capture component is a teaching away from that of Swedberg, the derivitization of a substrate surface for immobilization of protein such as antigen or antibody for use as a capture component is well within ordinary skill, as is likewise, taught and suggested by Isaka in column 3, lines 6-14 wherein an enzyme is immobilized in the porous channel.

Contrary to Applicant's argument, Swedberg also teaches various embodiments of detector configuration including the fabrication of a detector onto the substrate (see column 17, lines 31-45 and Figures 2-4).

D) Applicant argues that the combination of Isaka and Northrup with Miura et al. does not suggest or render obvious claims 14, 15, 17, and 21 because Miura et al. does not disclose a vacuum source in communication with a column as recited in the rejected claims.

Contrary to Applicant's argument, Miura, indeed, discloses a miniaturized sample separator that includes sample gas or vacuum source fed under pressure by a feed pump through the channel flowpath.

E) Applicant argues that the combination of Isaka and Northrup with Sunzeri does not suggest or render obvious claims 14, 15, 17, and 21 because Sunzeri does not disclose using at least one of the multiple, distinct, unconnected capillary columns as suggested by Northrup, as control or standard columns. Applicant specifically argues that Sunzeri does not teach or suggest "a parallel control column" as claimed, in a "parallel miniature chromatographic column".

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a parallel control column or parallel miniature chromatographic column) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, it is well known in the art of chromatography, i.e. affinity chromatography, to assay samples and controls in parallel columns so as to evaluate extent of accuracy of an assay.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was

within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:30 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
July 20, 2004

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7/24/04